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Description

This invention relates to pharmaceutical compositions of ibuprofen for oral administration. More particularly, the invention relates to pharmaceutical powder and tablet compositions containing ibuprofen or a salt thereof which effervesce when added to water, forming an aqueous suspension of ibuprofen suitable for oral administration. Such aqueous suspensions are convenient in use and are advantageous for those patients, often children and elderly patients, who have difficulty in swallowing tablets or capsules.

Ibuprofen, the chemical name of which is 2-(4-isobutylphenyl)propionic acid, is a well known medicament with anti-inflammatory, antipyretic and analgesic activities. The uses of ibuprofen include the treatment of pain and inflammation in musculoskeletal disorders such as rheumatic disease, and the treatment of pain in a variety of other disorders.

US Patent No. 4414198 relates to a rapidly water-disintegrable tablet comprising an active ingredient such as a foodstuff or a medicament, combined with a tablet disintegrable system comprising an unreacted, intimate mixture of alginic acid and a water soluble metal carbonate. The ingredients are combined by intimate mixing of all components and then formed into a tablet.

The present invention provides a pharmaceutical composition in powder or tablet form comprising:

a) a granular component comprising an intimate mixture of:

i) ibuprofen or a pharmaceutically acceptable salt thereof;

ii) a pharmaceutically acceptable water-insoluble hydrophilic polymer;

iii) a first part of an effervescent couple that produces carbon dioxide in the presence of water; and

b) a powder component comprising a second part of the effervescent couple;

the composition further comprising a pharmaceutically acceptable anionic or non-ionic surfactant and, preferably, a saccharide, each of which may be incorporated in the granular component or the powder component.

The compositions of the present invention effervesce when added to water, producing an aqueous suspension of ibuprofen which can be swallowed by a patient as the effervescence continues.

We have found that the inclusion of the water-insoluble hydrophilic polymer in the compositions of the present invention gives an improved suspension of ibuprofen or salt thereof when the compositions of the present invention are added to water. This has the advantageous result that, when a patient has consumed an aqueous suspension of ibuprofen or salt thereof prepared from a composition of the present invention, only a small amount of particles of ibuprofen or salt thereof is left as a residue on the sides of the drinking vessel used by the patient. In the absence of the water-insoluble hydrophilic polymer, the amount of ibuprofen or salt thereof left as a residue is unacceptably large and is also more variable from one occasion to the next.

The powder compositions of the present invention may be prepared by a process which comprises mixing the components of the granular component (a) to form granules and mixing the granules with the remainder of the composition. The tablets of the present invention may be prepared by compressing the mixture so obtained.

The term "water-insoluble" denotes a hydrophilic polymer that, in powder form, has little or no solubility in water at ambient temperatures under the conditions of use of the compositions of the present invention.

Suitable hydrophilic polymers include starch, for example maize starch; cellulose for example powdered cellulose and microcrystalline cellulose; water-insoluble modified starches for example sodium carboxymethyl starch; water-insoluble cellulose derivatives, for example croscarmellose sodium (cross-linked sodium carboxymethyl cellulose); cross-linked polyvinylpyrrolidone and alginic acid. A preferred hydrophilic polymer is microcrystalline cellulose, for example the products sold as Avicel PH-101 and Avicel PH-102 (Avicel is a Trade Mark) by the FMC Corporation of Philadelphia, Pennsylvania, USA. Another preferred hydrophilic polymer is croscarmellose sodium, for example the product sold as Ac-Di-Sol (Ac-Di-Sol is a Trade Mark) by the FMC Corporation.

Two or more water-insoluble hydrophilic polymers may be incorporated in the compositions of the present invention. A preferred mixture is croscarmellose sodium and microcrystalline cellulose, for example in the ratio (parts by weight) of 1:10 to 10:1. More preferred is a mixture of 1 part croscarmellose sodium to 1-10 parts, preferably 3-7 parts and especially 5 parts of microcrystalline cellulose.

The surfactant used in the compositions of the present invention is anionic or non-ionic. The surfactant preferably has an HLB (hydrophilic-lipophilic balance) value greater than 10.0, for example greater than 12.0 and more particularly greater than 13.0. The surfactant may be a solid or liquid and a single surfactant or more than one surfactant may be used.

Suitable anionic surfactants include sodium lauroylsarcosinate and sodium lauryl sulphate. A preferred anionic surfactant is sodium lauryl sulphate, which is a solid material.

Preferred nonionic surfactants include ethoxylated lauric esters of polyhydric alcohols, for example, polyoxyethylene glycol monolaurates with 4-20 ethylene oxide units per molecule and polyoxyethylene sorbitan monolaurates with 4-20 ethylene oxide units per molecule. One example is Tween 20 (Tween is a Trade Mark), which is a liquid polyoxyethylene sorbitan monolaurate with 20 ethylene oxide units per molecule, available from Atlas Chemical Industries (UK) Ltd. of Leatherhead, United Kingdom.

Pharmaceutically acceptable effervescent couples that produce carbon dioxide in the presence of water are well known in the art. One component of the effervescent couple is suitably a pharmaceutically acceptable solid acid, for example a solid organic acid such as citric acid, tartaric acid, adipic acid or malic acid. One or more acids may be used. The other component of the effervescent couple is suitably sodium carbonate, sodium bicarbonate, potassium carbonate or potassium bicarbonate, or a mixture thereof. The amounts of the components of the effervescent couple are generally chosen so that the pH of the aqueous mixture that results when the compositions of the present invention are added to water is below 7.0, preferably between 3.0 and 5.0 and especially between 3.0 and 4.0.

It has been found that the incorporation of a saccharide in the compositions of the present invention improves the stability of the compositions and gives compositions with an improved shelf life. Suitable saccharides include, for example, sucrose, lactose, dextrose and sorbitol. Lactose and sucrose are preferred saccharides. Sucrose is especially preferred.

It is preferred to incorporate the saccharide in finely powdered form into the compositions of the present invention. The amount of saccharide used is generally within the range of 0.5 to 20, preferably 1 to 10 and especially 4 to 7 parts by weight of saccharide to 1 part by weight of ibuprofen or salt thereof.

In the compositions of the present invention the ibuprofen or salt thereof and the hydrophilic polymer are in intimate admixture and are contained in granules comprising a mixture of the ibuprofen or salt thereof, the hydrophilic polymer and one component of the effervescent couple. Powder compositions are particularly preferred.

The powder compositions of the present invention are granules comprising ibuprofen or salt thereof, a water-insoluble hydrophilic polymer and one component of the effervescent couple, preferably the acid component, these granules being mixed with a separate powder comprising the other component of the effervescent couple. The surfactant may be included in the granules containing the ibuprofen or salt thereof or may be incorporated in the remainder of the composition. The saccharide is preferably included in the granules containing the ibuprofen or salt thereof but may alternatively be included in the remainder of the composition. These compositions are prepared by granulation and mixing processes that are well known in the art. It will be appreciated that, since both components of the effervescent couple are not present in the same granule, aqueous or non-aqueous solvents may be used in a wet granulation process to prepare the granules.

For example, a mixture of dry powder ingredients comprising ibuprofen or a salt thereof, water-insoluble hydrophilic polymer, one component of the effervescent couple, and preferably also a saccharide is prepared. The mixture is wet granulated, for example by treatment with a solution of a binding agent such as polyvinylpyrrolidone in a nonaqueous solvent such as isopropanol. The granules are dried, sieved to an appropriate size, and mixed with a dry powder comprising the other component of the effervescent couple, the surfactant and, if desired, one or more flavouring agents.

The compositions of the present invention may contain a salt of ibuprofen, but preferably contain ibuprofen itself. If a water-soluble salt of ibuprofen, for example the sodium or potassium salt, is used, the salt reacts with the acid component of the effervescent couple when the composition is added to water, causing at least some of the ibuprofen to precipitate and thus forming an aqueous suspension of ibuprofen. If a water-insoluble salt of ibuprofen, for example the calcium or aluminium salt, is used, a suspension of this salt is obtained when the composition is added to water.

For use by the patient, the powder compositions of the present invention are packaged in unit dosage form, for example in sachets made of material that is impervious to water. It will be appreciated that the compositions must be packaged so as to protect them from atmospheric moisture.

The tablet compositions of the present invention may be prepared by compressing a powder composition of the present invention, i.e. a mixture comprising a granular component comprising ibuprofen or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable water-insoluble hydrophilic polymer, and one component of a pharmaceutically acceptable effervescent couple that produces carbon dioxide in the presence of water and a powder component comprising the other component of the effervescent couple, the powder composition further comprising a pharmaceutically acceptable surfactant and, preferably, a saccharide, each of which may be incorporated in the granular or powder component. Conventional tabletting methods may be used. It may be desirable to incorporate conventional tablet excipients for example a binding agent, for example polyvinylpyrrolidone and/ or a lubricant, for example

polyethylene glycol 6000 in the powder composition prior to tabletting. It will be appreciated that the tablets of the present invention must be protected from atmospheric moisture. This can be done, for example, by packaging the tablets in individual compartments in a cold-formed blister pack or foil strip.

The compositions of the present invention in unit dosage form suitably contain 50-1200 mg, more usually 200-800 mg ibuprofen or the therapeutic equivalent of a pharmaceutically acceptable salt of ibuprofen.

The compositions of the present invention suitably contain, per 100 parts (parts by weight) ibuprofen or pharmaceutically acceptable salt thereof, 5-100 parts, preferably 10-50 parts and especially 20-40 parts of water-soluble hydrophilic polymer and 0.01-20 parts surfactant and preferably also 50-2000, especially 100-1000 parts of saccharide. In the case of an anionic surfactant, the preferred amount is 0.01-10 parts, especially 0.1-1.0 parts. In the case of a nonionic surfactant, the preferred amount is 0.1-20 parts, especially 0.5-10 parts.

A preferred pharmaceutical powder composition comprises, in parts by weight, 100 parts ibuprofen, a pharmaceutically acceptable effervescent couple that produces carbon dioxide in the presence of water, 0.01 to 20 parts of a pharmaceutically acceptable anionic or non-ionic surfactant, the ibuprofen being contained in granules comprising a mixture of 100 to 1000 parts sucrose and 10 to 50 parts of a mixture of 1 part croscarmellose sodium and 1 to 10 parts of microcrystalline cellulose.

The following Examples illustrate the invention.

Example 1

A powder composition was prepared from the following ingredients.

Ingredient	Weight in grams
Ibuprofen B.P.	1575.0
Microcrystalline cellulose (a)	375.0
Croscarmellose sodium (b)	75.0
Polyvinylpyrrolidone (c)	100.0
Malic acid B.P.	4125.0
Sodium saccharin B.P.	62.5
Sodium bicarbonate B.P. coarse granules	2250.0
Anhydrous sodium carbonate	375.0
Sodium lauryl sulphate B.P.	7.5
Flavour	350.0
Isopropanol	q.s
Purified water B.P.	q.s

(a) Avicel PH-101
(b) Ac-Di-Sol
(c) Plasdone K29-32 supplied by GAF (Great Britain) Ltd., of Manchester, UK.

The ibuprofen, microcrystalline cellulose, croscarmellose sodium and malic acid were deaggregated by passage through a 1mm aperture sieve (16 mesh) and blended in a mixer. To a solution of the polyvinylpyrrolidone in isopropanol (500 ml) was added a solution of the sodium saccharin in Purified water B.P. (100 ml). This liquid was used to granulate the powder mixture described above, more isopropanol added as required. The wet granulate was passed through a 4mm aperture sieve (4 mesh) and dried in a stream of warm air in a fluid bed dryer to a water content less than 0.3% ^{w}/w. The dried granules were screened through a 0.5mm aperture sieve (30 mesh) and blended with the sodium bicarbonate, anhydrous sodium carbonate, sodium lauryl sulphate and orange flavour to give a uniform mixture. Before blending, the sodium bicarbonate was screened through a 0.5mm aperture sieve (30 mesh) whereas the anhydrous sodium carbonate, sodium lauryl sulphate and orange flavour were screened through a 0.25mm aperture sieve (60 mesh). All sieve sizes referred to are British Standard sizes. The resulting powder mixture was packed into water-impervious sachets each containing 630 mg ibuprofen.

The packed sachets were subjected to a storage test at 40° C. After 1 day at this temperature the powder composition had become agglomerated and sticky. Thus the composition was unsatisfactory after storage for 1 day at 40° C.

Example 2

A powder composition was prepared from the following ingredients.

Ingredient	Parts by weight
Ibuprofen B.P.	600
Microcystalline cellulose (a)	150
Croscarmellose sodium (b)	30
Sucrose fine powder	3500
Polyvinylpyrrolidone (c)	10
Malic acid granular	1650
Sodium saccharin B.P.	25
Sodium Bicarbonate B.P. coarse granules	500
Anhydrous sodium carbonate	150
Sodium lauryl sulphate B.P.	3
Orange Flavour	140

(a) Avicel PH-101
(b) Ac-Di-Sol
(c) Plasdone K29-32

The ibuprofen, microcrystalline cellulose, croscarmellose sodium, malic acid, sucrose were deaggregated by passage through a 1mm aperture sieve (16 mesh) and blended together with the sodium saccharin in a mixer. The mixture was granulated with a solution of the polyvinylpyrrolidone in isopropanol. The resulting granules were dried, screened through a 0.5mm aperture sieve (30 mesh) and blended with the remaining ingredients to give a uniform mixture. Before blending, the sodium bicarbonate was screened through a 0.5mm sieve (30 mesh) whereas the anhydrous sodium carbonate, sodium lauryl sulphate and orange flavour were screened through a 0.25mm aperture sieve (60 mesh). All sieve sizes referred to are British Standard sizes. The resulting powder mixture was packed into water-impervious sachets each containing 600 mg ibuprofen.
The composition was examined after five months storage in a water-impervious closed container at 30° C and 40° C and found to be satisfactory.

Example 3

A powder composition was prepared from the following ingredients.

Ingredient	Parts by weight
Ibuprofen sodium salt dihydrate	807
Microcrystalline cellulose (a)	150
Croscarmellose sodium (b)	30
Polyvinylpyrrolidone (c)	40
Malic acid granular	1650
Sodium saccharin B.P.	25
Sodium bicarbonate B.P. coarse granules	900
Anhydrous sodium carbonate	150
Sodium lauryl sulphate B.P.	3
Orange Flavour	140

(a) Avicel PH-101
(b) Ac-Di-Sol
(c) Plasdone K29-32

In a similar manner to that described in Example 2, granules were prepared containing the ibuprofen sodium salt, microcrystalline cellulose, croscarmellose sodium, malic acid and sodium saccharin. In a similar manner to that described in Example 2, these granules were blended with the remaining ingredients

and the resulting mixture was packed into water-impervious sachets each containing 800 mg ibuprofen sodium salt. In a storage test of the sachets at 30° C, the composition was found to be satisfactory after 85 days In storage tests at 40° C, the composition was found to be satisfactory after 40 days but unsatisfactory thereafter, as shown by agglomeration of the powder composition.

Example 4

Powder formulations were prepared as described in Example 2, except that the sucrose in the formulation was replaced with the same quantity of one of the following saccharides in the form of a fine powder.

(a) lactose B.P.
(b) dextrose monohydrate b.p.
(c) sorbitol

The resulting powder formulations were packed into water-impervious closed containers and subjected to storage tests at 30° C and 40° C. The following results were obtained.

Composition	Time in months(m) or days(d) at which composition became unsatisfactory at temperature	
	30° C	40° C
(a)	>3m	>3m
(b)	>24d <3m	>24d <3m
(c)	>24d <3m	17d

The result >3m signifies that the formulation was satisfactory when examined after 3 months. The result >24d <3m signifies that the composition was satisfactory when examined at 24 days but unsatisfactory (agglomeration of powder to a sticky solid) when examined after 3 months.

Example 5

Powder formulations were prepared as described in Example 2, except that the amount of sucrose in the formulation was altered to the following amounts.

(a) 630 parts weight
(b) 6300 parts weight.

The resulting formulations were packed into water-impervious closed containers and subjected to storage tests at 30° C and 40° C. The following results were obtained.

Composition	Time in months(m) or days(d) at which composition became unsatisfactory at temperature	
	30° C	40° C
(a)	>3m	24d
(b)	>24d <3m	>24d <3m

Example 6

A powder formulation was prepared as described in Example 2, except that the sucrose powder was not included in the granules but was blended with the remaining ingredients after granulation. The resulting formulation was packed into a water-impervious closed container and was subjected to storage tests at 30° C and 40° C and the composition was found to be satisfactory after 3 months storage at these temperatures.

Example 7

A powder composition is prepared from the following ingredients.

Ingredient	Parts by weight
Ibuprofen	600
Maize starch B.P.	150
Malic acid granular	1650
Sodium saccharin	18
Polyvinylpyrrolidone (a)	40
Empilan AQ 100 (b)	10
Sodium bicarbonate	900
Anhydrous sodium carbonate coarse granules	150
Orange Flavour	140

(a) Plasdone K29-32
(b) A polyoxyethylene glycol monolaurate from Albright and Wilson Ltd. of Whitehaven, Cumbria, U.K.

In a similar manner to that described in Example 1, a mixture of the ibuprofen, maize starch and malic acid is granulated with a solution of the sodium saccharin and polyvinylpyrrolidone in aqueous isopropanol. The granules are dried and blended with the remaining ingredients. The mixture is packed into water-impervious sachets each containing 600 mg ibuprofen.

Example 8

A powder composition is prepared as described in Example 7 except that the maize starch is replaced by the same amount of microcrystalline cellulose (Avicel PH-101). The resulting powder is packed into water-impermeable sachets each containing 600 mg ibuprofen.

Example 9

A powder composition is prepared from the following ingredients.

Ingredient	Parts by weight
Ibuprofen B.P.	300
Microcrystalline cellulose (a)	75
Croscarmellose sodium (b)	15
Sucrose fine powder	1750
Malic acid granular	825
Sodium saccharin B.P.	12.5
Polyvinylpyrrolidone (c)	5
Sodium bicarbonate B.P. coarse granules	450
Anhydrous sodium carbonate	75
Orange Flavour	70
Sodium lauryl sulphate	1.5

(a) Avicel PH-101
(b) Ac-Di-Sol
(c) Plasdone K29-32

The method used is similar to that described in Example 2. Granules are prepared containing the ibuprofen, microcrystalline cellulose, croscarmellose sodium, malic acid, sucrose sodium saccharin and polyvinylpyrrolidone. The resulting granules are blended with the remaining ingredients and the mixture is compressed into tablets containing 300 mg ibuprofen. The tablets are packed into water-impervious foil strips.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition in powder or tablet form comprising:

   a) a granular component comprising an intimate mixture of:
      i) ibuprofen or a pharmaceutically acceptable salt thereof;
      ii) a pharmaceutically acceptable water-insoluble hydrophilic polymer;
      iii) a first part of an effervescent couple that produces carbon dioxide in the presence of water; and
   b) a powder component comprising a second part of the effervescent couple;

   the composition further comprising a pharmaceutically acceptable anionic or non-ionic surfactant and, preferably, a saccharide, each of which may be incorporated in the granular component or the powder component.

2. A pharmaceutical composition according to claim 1 comprising, in parts by weight, 5 to 100 parts hydrophilic polymer and 50 to 2000 parts saccharide per 100 parts ibuprofen or salt thereof.

3. A pharmaceutical composition according to claim 2 wherein the hydrophilic polymer comprises microcrystalline cellulose and the saccharide comprises sucrose or lactose.

4. A pharmaceutical composition according to claim 3 in which the pharmaceutically acceptable water-insoluble hydrophilic polymer is a mixture of croscarmellose sodium and microcrystalline cellulose in the ratio by weight of 1:10 to 10:1.

5. A pharmaceutical composition according to claim 4 in which the mixture comprises 1 part croscarmellose sodium to 1 to 10 parts microcrystalline cellulose.

6. A pharmaceutical composition according to claim 5 wherein the mixture comprises 1 part croscarmellose sodium to 3 to 7 parts microcrystalline cellulose.

7. A pharmaceutical composition according to any one of the preceding claims in which the amounts of the first and second parts of the effervescent couple are such that when the pharmaceutical composition is added to water, the resulting pH is below 7.

8. A pharmaceutical powder composition according to claim 1 comprising, in parts by weight, 100 parts ibuprofen, a pharmaceutically acceptable effervescent couple that produces carbon dioxide in the presence of water, 0.01 to 20 parts of a pharmaceutically acceptable anionic or non-ionic surfactant, the ibuprofen being contained in granules comprising a mixture of 100 to 1000 parts sucrose and 10 to 50 parts of a mixture of 1 part croscarmellose sodium and 1 to 10 parts of microcrystalline cellulose.

9. A pharmaceutical powder composition according to claim 8 wherein the surfactant is sodium lauryl sulphate or a polyoxyethylene sorbitan monolaurate with 4 to 20 ethylene oxide units per molecule.

10. A pharmaceutical composition in powder or tablet form comprising:

   a) a granular component comprising an intimate mixture of:
      i) ibuprofen or a pharmaceutically acceptable salt thereof;
      ii) a pharmaceutically acceptable water-insoluble hydrophilic polymer;
      iii) a first part of an effervescent couple that produces carbon dioxide in the presence of water; and
      iv) a saccharide
   b) a powder component comprising a second part of the effervescent couple and a pharmaceutically acceptable anionic or non-anionic surfactant.

11. A process for the preparation of a pharmaceutical powder or tablet composition according to any one of claims 1 to 10 which comprises mixing the components of the granular component to form granules, then mixing the granules with the powder component of the composition and, if desired, compressing the mixture so obtained to form tablets.

Claims for the following Contracting States : AT, GR, ES

1. A process to form a pharmaceutical composition in powder or tablet form comprising:

a) a granular component comprising an intimate mixture of:
i) ibuprofen or a pharmaceutically acceptable salt thereof;
ii) a pharmaceutically acceptable water-insoluble hydrophilic polymer;
iii) a first part of an effervescent couple that produces carbon dioxide in the presence of water; and
b) a powder component comprising a second part of the effervescent couple;

the composition further comprising a pharmaceutically acceptable anionic or non-ionic surfactant and, preferably, a saccharide, each of which may be incorporated in the granular component or the powder component, which comprises mixing the components of the granular component to form granules, then mixing the granules with the powder component of the composition and, if desired, compressing the mixture so obtained to form tablets.

2. A process according to claim 1 wherein the composition comprises in parts by weight, 5 to 100 parts hydrophilic polymer and 50 to 2000 parts saccharide per 100 parts ibuprofen or salt thereof.

3. A process according to claim 2 wherein the hydrophilic polymer comprises microcrystalline cellulose and the saccharide comprises sucrose or lactose.

4. A process according to claim 3 in which the pharmaceutically acceptable water-insoluble hydrophilic polymer is a mixture of croscarmellose sodium and microcrystalline cellulose in the ratio by weight of 1:10 to 10:1.

5. A process according to claim 4 in which the mixture comprises 1 part croscarmellose sodium to 1 to 10 parts microcrystalline cellulose.

6. A process according to claim 5 wherein the mixture comprises 1 part croscarmellose sodium to 3 to 7 parts microcrystalline cellulose.

7. A process according to any one of the preceding claims in which the amounts of the first and second parts of the effervescent couple are such that when the pharmaceutical composition is added to water, the resulting pH is below 7.

8. A process according to claim 1 wherein the pharmaceutical powder composition comprises, in parts by weight, 100 parts ibuprofen, a pharmaceutically acceptable effervescent couple that produces carbon dioxide in the presence of water, 0.01 to 20 parts of a pharmaceutically acceptable anionic or non-ionic surfactant, the ibuprofen being contained in granules comprising a mixture of 100 to 1000 parts sucrose and 10 to 50 parts of a mixture of 1 part croscarmellose sodium and 1 to 10 parts of microcrystalline cellulose.

9. A process according to claim 8 wherein the surfactant is sodium lauryl sulphate or a polyoxyethylene sorbitan monolaurate with 4 to 20 ethylene oxide units per molecule.

10. A process as claimed in any one of claims 1-9 to form a pharmaceutical composition in powder or tablet form comprising:

a) a granular component comprising an intimate mixture of:
i) ibuprofen or a pharmaceutically acceptable salt thereof;
ii) a pharmaceutically acceptable water-insoluble hydrophilic polymer;
iii) a first part of an effervescent couple that produces carbon dioxide in the presence of water; and
iv) a saccharide
b) a powder component comprising a second part of the effervescent couple and a pharmaceutically acceptable anionic or non-anionic sufactant.

which comprises mixing the components of the granular component to form granules, then mixing the granules with the powder component of the composition and, if desired, compressing the mixture so obtained to form tablets.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique, sous forme de poudre ou de comprimé, qui comprend :

   a) un composant granulaire, constitué d'un mélange intime :
      i) d'ibuprofène ou d'un sel pharmaceutiquement acceptable de celui-ci,
      ii) d'un polymère hydrophile, insoluble dans l'eau, pharmaceutiquement acceptable,
      iii) d'une première partie d'un couple effervescent qui engendre de l'anhydride carbonique en présence d'eau et
   b) un composant pulvérulent ou en poudre comprenant une seconde partie du couple effervescent,

   la composition comprenant, en outre, un agent tensioactif ou surfactif anionique ou non ionique, pharmaceutiquement acceptable et, de préférence, un saccharide, chacun d'entre eux pouvant être incorporé au composant granulaire ou au composant pulvérulent.

2. Composition pharmaceutique suivant la revendication 1, comprenant, en parties en poids, 5 à 100 parties du polymère hydrophile et 5 à 2000 parties de saccharide par 100 parties d'ibuprofène ou de son sel.

3. Composition pharmaceutique suivant la revendication 2, caractérisé en ce que le polymère hydrophile est constitué de cellulose microcristalline et le saccharide est constitué de saccharose ou de lactose.

4. Composition pharmaceutique suivant la revendication 3, caractérisée en ce que le polymère hydrophile, insoluble dans l'eau, pharmaceutiquement acceptable, est un mélange de croscarmellose sodique et de cellulose microcristalline dans le rapport pondéral de 1:10 à 10:1.

5. Composition pharmaceutique suivant la revendication 4, caractérisée en ce que le mélange comprend une partie de croscarmellose sodique pour 1 à 10 parties de cellulose microcristalline.

6. Composition pharmaceutique suivant la revendication 5, caractérisée en ce que le mélange comprend une partie de croscarmellose sodique pour 3 à 7 parties de cellulose microcristalline.

7. Composition pharmaceutique suivant l'une quelconque des revendications précédentes, caractérisée en ce que les proportions de la première et de la seconde parties du couple effervescent sont telles que lorsque l'on ajoute la composition pharmaceutique à de l'eau, le pH qui en résulte soit inférieur à 7.

8. Composition pharmaceutique pulvérulente ou en poudre, suivant la revendication 1, comprenant, en parties en poids, 100 parties d'ibuprofène, un couple effervescent, pharmaceutiquement acceptable, qui engendre de l'anhydride carbonique en présence d'eau, 0,01 à 20 parties d'un agent tensioactif ou surfactif anionique ou non ionique, pharmaceutiquement acceptable, l'ibuprofène étant contenu dans des granules comprenant un mélange de 100 à 1000 parties de saccharose et de 10 à 50 parties d'un mélange de 1 partie de croscarmellose sodique et de 1 à 10 parties de cellulose microcristalline.

9. Composition pharmaceutique pulvérulente ou en poudre, suivant la revendication 8, caractérisée en ce que l'agent tensioactif ou surfactif est le laurylsulfate de sodium ou un monolaurate de polyoxyéthylènesorbitan avec 4 à 20 unités oxyde d'éthylène par molécule.

10. Composition pharmaceutique, sous forme de poudre ou de comprimé, qui comprend
    a) un composant granulaire constitué d'un mélange intime
       i) d'ibuprofène ou d'un sel pharmaceutiquement acceptable de celui-ci,
       ii) d'un polymère hydrophile, insoluble dans l'eau, pharmaceutiquement acceptable,
       iii) d'une première partie d'un couple effervescent qui engendre de l'anhydride carbonique en

présence d'eau et
iv) d'un saccharide,
b) un composant en poudre ou pulvérulent comprenant une seconde partie du couple effervescent et un agent tensioactif ou surfactif anionique ou non anionique, pharmaceutiquement acceptable.

11. Procédé de préparation d'une composition pharmaceutique, sous forme de poudre ou de comprimé, suivant l'une quelconque des revendications 1 à 10, caractérisé en ce que l'on mélange les composants du constituant granulaire pour former des granules, puis on mélange les granules au constituant en poudre ou pulvérulent de la composition et, si on le souhaite, on comprime le mélange ainsi obtenu pour former des comprimés.

Revendications pour les Etats contractants suivants : AT, GR, ES

1. Procédé de confection d'une composition pharmaceutique, sous forme de poudre ou de comprimé, qui comprend :

a) un composant granulaire, constitué d'un mélange intime :
i) d'ibuprofène ou d'un sel pharmaceutiquement acceptable de celui-ci,
ii) d'un polymère hydrophile, insoluble dans l'eau, pharmaceutiquement acceptable,
iii) d'une première partie d'un couple effervescent qui engendre de l'anhydride carbonique en présence d'eau et
b) un composant pulvérulent ou en poudre comprenant une seconde partie du couple effervescent,

la composition comprenant, en outre, un agent tensioactif ou surfactif anionique ou non ionique, pharmaceutiquement acceptable et, de préférence, un saccharide, chacun d'entre eux pouvant être incorporé au composant granulaire ou au composant pulvérulent, caractérisé en ce que l'on mélange les composants du constituant granulaire pour former des granules, puis on mélange les granules au constituant en poudre ou pulvérulent de la composition et, si on le souhaite, on comprime le mélange ainsi obtenu pour former des comprimés.

2. Procédé suivant la revendication 1, caractérisé en ce que la composition comprend en parties en poids, 5 à 100 parties du polymère hydrophile et 5 à 2000 parties de saccharide par 100 parties d'ibuprofène ou de son sel.

3. Procédé suivant la revendication 2, caractérisé en ce que le polymère hydrophile est constitué de cellulose microcristalline et le saccharide est constitué de saccharose ou de lactose.

4. Procédé suivant la revendication 3, caractérisé en ce que le polymère hydrophile, insoluble dans l'eau, pharmaceutiquement acceptable, est un mélange de croscarmellose sodique et de cellulose microcristalline dans le rapport pondéral de 1:10 à 10:1.

5. Procédé suivant la revendication 4, caractérisé en ce que le mélange comprend une partie de croscarmellose sodique pour 1 à 10 parties de cellulose microcristalline.

6. Procédé suivant la revendication 5, caractérisé en ce que le mélange comprend une partie de croscarmellose sodique pour 3 à 7 parties de cellulose microcristalline.

7. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que les proportions de la première et de la seconde parties du couple effervescent sont telles que lorsque l'on ajoute la composition pharmaceutique à de l'eau, le pH qui en résulte soit inférieur à 7.

8. Procédé suivant la revendication 1, caractérisé en ce que la composition pharmaceutique en poudre ou pulvérulente comprend en parties en poids, 100 parties d'ibuprofène, un couple effervescent, pharmaceutiquement acceptable, qui engendre de l'anhydride carbonique en présence d'eau, 0,01 à 20 parties d'un agent tensioactif ou surfactif anionique ou non ionique, pharmaceutiquement acceptable, l'ibuprofène étant contenu dans des granules comprenant un mélange de 100 à 1000 parties de saccharose et de 10 à 50 parties d'un mélange de 1 partie de croscarmellose sodique et de 1 à 10 parties de cellulose microcristalline.

erzeugt, 0,01 bis 20 Teile eines pharmazeutisch annehmbaren anionischen oder nichtionischen, oberflächenaktiven Mittels umfasst, wobei das Ibuprofen in Granula enthalten ist, die eine Mischung aus 100 bis 1000 Teilen Sucrose und 10 bis 50 Teilen einer Mischung aus 1 Teil Natriumcroscarmellose und 1 bis 10 Teilen mikrokristalliner Zellulose umfassen.

9. Pharmazeutische Pulverzusammensetzung nach Anspruch 8, worin das oberflächenaktive Mittel Natriumlaurylsulfat oder ein Polyoxyethylensorbitmonolaurat mit 4 bis 20 Ethylenoxideinheiten pro Molekül ist.

10. Pharmazeutische Zusammensetzung in Pulver- oder Tablettenform umfassend:

a) eine Granulatkomponente, aus einer innigen Mischung von:
i) Ibuprofen oder dessen pharmazeutisch annehmbaren Salzen;
ii) einem pharmazeutisch annehmbaren, wasserunlöslichen, hydrophilen Polymer;
iii) einem ersten Teil eines Brausepaares, das in Anwesenheit von Wasser Kohlendioxid erzeugt; und
iv) einem Saccharid
b) eine Pulverkomponente, die einen zweiten Teil des Brausepaares umfasst und ein pharmazeutisch annehmbares, anionisches oder nichtanionisches, oberflächenaktives Mittel umfasst.

11. Verfahren zur Herstellung einer pharmazeutischen Pulver- oder Tablettenzusammensetzung nach einem der Ansprüche 1 bis 10, wobei man die Komponenten der Granulatkomponente unter Bildung von Granula mischt, die Granula dann mit der Pulverkomponente der Zusammensetzung mischt und gegebenenfalls die so erhaltene Mischung unter Bildung von Tabletten verpresst.

Patentansprüche für folgende Vertragsstaaten : AT, GR, ES

1. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung in Pulver- oder Tablettenform umfassend:

a) eine Granulatkomponente aus einer innigen Mischung von:
i) Ibuprofen oder dessen pharmazeutisch annehmbaren Salzen;
ii) einem pharmazeutisch annehmbaren, wasserunlöslichen, hydrophilen Polymer;
iii) einem ersten Teil eines Brausepaares, das in Anwesenheit von Wasser Kohlendioxid erzeugt; und
b) eine Pulverkomponente, die einen zweiten Teil des Brausepaares umfasst,

wobei die Zusammensetzung weiterhin ein pharmazeutisch annehmbares, anionisches oder nichtionisches, oberflächenaktives Mittel und vorzugsweise ein Saccharid umfasst, von denen jedes in die Granulatkomponente oder die Pulverkomponente eingelagert sein kann, wobei man die Komponenten der Granulatkomponente unter Bildung von Granula mischt, die Granula dann mit der Pulverkomponente der Zusammensetzung mischt und gegebenenfalls die so erhaltene Mischung unter Bildung von Tabletten verpresst.

2. Verfahren nach Anspruch 1, bei dem die Zusammensetzung, in Gewichtsteilen, 5 bis 100 Teile hydrophiles Polymer und 50 bis 2000 Teile Saccharid pro 100 Teile Ibuprofen oder dessen Salze umfasst.

3. Verfahren nach Anspruch 2, bei dem das hydrophile Polymer mikrokristalline Zellulose und das Saccharid Sucrose oder Lactose umfasst.

4. Verfahren nach Anspruch 3, in dem das pharmazeutisch annehmbare, wasserunlösliche, hydrophile Polymer eine Mischung von Natriumcroscarmellose und mikrokristalliner Zellulose im Gewichtsverhältnis 1:10 bis 10:1 ist.

5. Verfahren nach Anspruch 4, bei dem die Mischung 1 Teil Natriumcroscarmellose zu 1 bis 10 Teilen mikrokristalliner Zellulose umfasst.

6. Verfahren nach Anspruch 5, bei dem die Mischung 1 Teil Natriumcroscarmellose zu 3 bis 7 Teilen mikrokristalliner Zellulose umfasst.

7. Verfahren, nach einem der vorstehenden Ansprüche, bei dem die Mengen der ersten und zweiten Teile des Brausepaares so sind, daß, wenn die pharmazeutische Zusammensetzung zu Wasser gegeben wird, der resultierende pH unter 7 ist.

8. Verfahren nach Anspruch 1, bei dem die pharmazeutische Pulverzusammensetzung, in Gewichtsteilen, 100 Teile Ibuprofen, ein pharmazeutisch annehmbares Brausepaar, das in Anwesenheit von Wasser Kohlendioxid erzeugt, 0,01 bis 20 Teile eines pharmazeutisch annehmbaren anionischen oder nichtionischen, oberflächenaktiven Mittels umfasst, wobei das Ibuprofen in Granula enthalten ist, die eine Mischung aus 100 bis 1000 Teilen Sucrose und 10 bis 50 Teilen einer Mischung aus 1 Teil Natriumcroscarmellose und 1 bis 10 Teilen mikrokristalliner Zellulose umfassen.

9. Verfahren nach Anspruch 8, bei dem das oberflächenaktive Mittel Natriumlaurylsulfat oder ein Polyoxyethylensorbitmonolaurat mit 4 bis 20 Ethylenoxideinheiten pro Molekül ist.

10. Verfahren nach einem der Ansprüche 1-9 zur Herstellung einer pharmazeutischen Zusammensetzung in Pulver- oder Tablettenform umfassend:

a) eine granulierte Komponente aus einer innigen Mischung von:
i) Ibuprofen oder dessen pharmazeutisch annehmbaren Salzen;
ii) einem pharmazeutisch annehmbaren, wasserunlöslichen, hydrophilen Polymer;
iii) einem ersten Teil eines Brausepaares, das in Anwesenheit von Wasser Kohlendioxid erzeugt; und
iv) einem Saccharid
b) eine Pulverkomponente, die einen zweiten Teil des Brausepaares und ein pharmazeutisch annehmbares, anionisches oder nichtanionisches, oberflächenaktives Mittel umfasst,

bei dem man die Komponenten der Granulatkomponente unter Bildung von Granula mischt, dann die Granula mit der Pulverkomponente der Zusammensetzung mischt und gegebenenfalls die so erhaltene Mischung unter Bildung von Tabletten verpresst.